Listing of Claims

1-157. (canceled)

158. (Currently Amended) A method for identifying a protein target as being able to bind a ligand ~~target to which a molecule is capable of binding~~, comprising:

(a) providing a ~~screening~~ molecule comprising a methotrexate moiety ~~or an analog of methotrexate~~ which binds to dihydrofolate reductase, covalently bonded to ~~a~~ the ligand ~~which has a specificity for an unknown protein target~~;

(b) introducing the ~~screening~~ molecule into a cell which i) expresses a first fusion protein comprising a dihydrofolate reductase ~~binding domain~~ capable of binding methotrexate, ii) a second fusion protein comprising the ~~unknown~~ protein target, wherein one of the first and second fusion proteins also comprises a transcription activator domain and the other comprises a DNA-binding domain, and iii) has a reporter gene, wherein expression of the reporter gene is conditioned on the proximity of the first fusion protein to the second fusion protein;

(c) permitting the ~~screening~~ molecule to bind to the first fusion protein and to the second fusion protein so as to activate the expression of the reporter gene; and

(d) selecting ~~which~~ the cell if it expresses the reporter gene, ~~; and~~

~~(c)~~ so as to thereby identify ~~identifying~~ the ~~unknown~~ protein target as being able to bind the ligand.

159. (Currently Amended) The method of claim 158, wherein the ~~unknown~~ protein target is encoded by a DNA from the group consisting of ~~genomicDNA, cDNA and syntheticDNA~~ genomic DNA, cDNA and synthetic DNA.

160. (Previously Presented) The method of claim 158, wherein the ligand has a known biological function.

161. (New) The method of claim 158, wherein the first fusion protein is (dihdrofolate reductase)-(DNA-binding domain).

162. (New) The method of claim 158, wherein the first fusion protein is (dihdrofolate reductase)-(LexA).

163. (New) The method of claim 158, wherein the first fusion protein is (dihdrofolate reductase)-(transcription activation domain).

164. (New) The method of claim 158, wherein the first fusion protein is (dihdrofolate reductase)-(B42).

165. (New) The method of claim 158, wherein the second fusion comprises a DNA-binding domain.

166. (New) The method of claim 158, wherein the second fusion protein comprises LexA.

167. (New) The method of claim 158, wherein the second fusion protein comprises a transcription activation domain.

168. (New) The method of claim 158, wherein the second fusion protein comprises B42.

169. (New) The method of claim 158, wherein the cell is S. cerevisiae or E. coli.

170. (New) The method of claim 158, wherein the reporter gene is lacZ, Gal4 or Ura-3.

171. (New) The method of claim 158, wherein the cell is a bacterial cell, the molecule comprises a methotrexate moiety bound to the ligand, the first fusion protein comprises a dihydrofolate reductase and a LexA, the second fusion protein comprises the protein target and B42, and the reporter gene is LacZ.

172. (New) The method of claim 158, wherein the cell is a yeast cell, the molecule comprises a methotrexate moiety bound to the ligand, the first fusion protein comprises a dihydrofolate reductase and a LexA, the second fusion protein comprises the protein target and B42, and the reporter gene is Gal4.

173. (New) A method for identifying a receptor as being able to bind a ligand comprising:

(a) providing a hybrid ligand comprising a methotrexate moiety which binds to dihydrofolate reductase covalently bonded to the ligand;

(b) introducing the molecule into a cell which i) expresses a first fusion protein comprising a dihydrofolate reductase and a DNA-binding domain,

ii) a second fusion protein comprising the receptor and a transcription activation domain, and iii) has a reporter gene, wherein activation of the reporter gene is conditioned on the proximity of the first fusion protein to the second fusion protein;

(c) permitting the molecule to bind to the first fusion protein and to the second fusion protein so as to activate the reporter gene; and

(d) selecting the cell having an activated reporter gene,

so as to thereby identify the receptor as being able to bind the ligand.

174. (New) The method of claim 173, wherein the first fusion protein is (dihdrofolate reductase)-(LexA).

175. (New) The method of claim 173, wherein the second fusion protein comprises B42.

176. (New) The method of claim 173, wherein the reporter gene is LacZ or Gal4.

177. (New) In a method for determining if a protein interacts with a ligand in vivo, wherein the method comprises activating a reporter gene by contacting a cell expressing two fusion proteins, the first comprising a ligand-binding domain fused to a DNA-binding domain and the second comprising a transcription activation domain fused to the protein, with a covalently linked hybrid-ligand so as to activate the reporter gene, the improvement comprising a covalently linked hybrid-ligand having a methotrexate moiety.

178. (New) The method of claim 177, wherein the DNA-binding domain is a LexA DNA-binding domain.

179. (New) The method of claim 177, wherein the transcription activation domain is B42.

180. (New) The method of claim 177, wherein the reporter gene is LacZ or Gal4.